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1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,145	MACKAY, CHARLES REAY	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,15,20 and 25-54* is/are pending in the application.

4a) Of the above claim(s) *40-51* is/are withdrawn from consideration.

5)☒ Claim(s) *29-32 and 52-54* is/are allowed.

6)☒ Claim(s) *1-10,15,20,25-28 and 33-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20090204*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a Rule 371 continuation of PCT Serial Number PCT/AU03/00084, which claims the benefit of the filing date of provisional U.S. Application 60/350,961.

Claims 11-14, 16-19, and 21-24 have been canceled.

New claims 52-54 have been added.

Claims 1-10, 15, 20, and 25-54 are currently pending.

Election/Restrictions

1. **Claims 40-51 stand withdrawn** from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on January 3, 2008.

Accordingly, **claims 1-10, 15, 20, 25-39 and 52-54 are the subject of examination** in the present Office Action.

In view of Applicant's response and amendment filed July 7, 2008 only the following ground of rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 10, 15, and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody comprising all six of the CDR regions of an antibody produced by one of the hybridomas disclosed as 00110609, 02090226 and 02090227, does not reasonably provide enablement for the broad recitation of an antibody comprising "substantially" the same heavy or light chain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention,

the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to antibodies that have heavy and light chains that are "substantially" the same as the heavy and light chains from one of the described monoclonal antibodies. However, the metes and bounds of "substantially" are not set forth in the claims or in the specification as originally filed. The term invites and encompasses change to the disclosed sequences. Such change is inclusive of the alteration or complete substitution of one or more of the six CDRs.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity that is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff (Proc Natl Acad Sci USA [1982] 79:1979-1983; U on form PTO-892). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function (see entire document).

MacCallum (J. Mol. Biol. [1996] 262:732-745; V on form PTO-892) analyzed a number of different antibodies for interactions with antigen and discloses that the CDR3s of the heavy and light chain dominate, however a number of residues outside the standard CDR definitions make antigen contacts (page 733, column 2 in particular) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (page 735, column 1 in particular).

Casset (Biochem. Biophys. Res. Comm. [2003] 307:198-205; W on form PTO-892) underscores the fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen-binding site as shown in the case of the construction of a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design. The peptide was designed with 27 residues formed

by residues from 5 CDRs (see entire document). Casset discloses that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, column 1 in particular) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (page 202, column 1 in particular).

Wu (J. Mol. Biol. [1999] 294:151-162; X on form PTO-892) discloses that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding but certain residues have been identified as important for maintaining conformation (page 152, column 1 in particular).

As there is no disclosure of residues within the CDRs that are critical and not amenable to change, the specification is not enabling for the full scope of the claimed invention because there is no guidance provided for the artisan as to which residues associated with the binding sites of the antibodies could be changed or must remain the same.

Accordingly, in view of the limited guidance provided by the specification, the level of predictability in the art, the nature of the claimed invention and the undue experimentation required of one of ordinary skill in the art, it would require an undue amount of trial and error to practice the full scope of the invention and this is not sanctioned by the statute.

The following represent NEW GROUNDS of rejection and necessitate that this Office Action be made NON-FINAL. In addition, the objection presented here is also new in the instant Office Action.

Claim Objections

1. Claims 2 is objected to because of the following informalities:

Claim 2 is objected to for the recitation of a segment of an amino acid sequence of C5aR without reciting the corresponding sequence identifier. It is noted that page 10 of the specification discloses that the sequence of C5aR is described as SEQ ID NO: 1. Accordingly, it is suggested that the claim be amended to recite --comprising the second extracellular loop ~~(residues 175 to 206)~~ of C5aR, residues 175 to 206 of SEQ ID NO: 1.--

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 10, 15 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially" is a relative term that renders the claims indefinite. The term "substantially" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 1, 2, 9, 25, 28, and 39 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Base claim 1 is drawn to "An antibody…" C5aR is a naturally occurring protein and antibodies to C5aR could occur naturally, for example as part of an autoimmune disease process. Accordingly, the claims read upon a product of nature and should be amended to recite --An <u>isolated</u> antibody…--.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-9, 25, 26, 36, 37 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Watanabe et al (J. Imm. Meth. [1995] 185:19-29; cited on form PTO-1449 filed 10/15/04).

Watanabe et al teaches 4C8, a monoclonal IgM antibody that is reactive with an extracellular region of the C5aR, but does not recognize the C5aR active site (Abstract in particular), which is known to reside on the N-terminal domain. Watanabe teaches the binding of the antibody to living cells, evidencing that the antibody binds to one of the extracellular loops. Watanabe also teaches the detection of 4C8 with FITC labeled anti-mouse antibody, satisfying the metes and bounds of a conjugate comprising a detectable label [claims 36, 37] (page 22, section 2.10, in particular). Watanabe teaches the washing of cells with 4C8 in PBS, which comprises water, a pharmaceutically acceptable carrier [claim 39] (page 22, section 2.10, in particular). Claim 9 is included because the method used to determine the antibody's ability to bind to C5aR does not affect the binding properties of the antibody. Claims 2 and 25 are included because, while Watanabe is silent about where in the extracellular loops the mAb 4C8 specifically binds [claim 2] and silent about the ability of the antibody to inhibit neutrophil attraction by means other than C5a [claim 25], silence about a particular property does not necessarily constitute the absence of that property. Claims 3-8 are included because, while Watanabe is silent regarding the extracellular epitope to which 4C8 binds, 4C8 may bind to the same epitope as one of the monoclonal antibodies as deposited with ECACC under accession number 00110609, accession number 02090226, or accession number 02090227. As stated previously, silence about a particular property does not necessarily constitute the absence of that property. Since Watanabe teaches that 4C8 does not bind to the N-terminal region but does inhibit C5a binding to the C5aR, the functional properties of 4C8 appear the same as those of 00110609, 02090226, and 02090227 and therefore the epitope that 4C8 binds to may also be the same. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the materials, i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is on the Applicant to prove that the claimed materials are different from t those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). The office has no way of knowing whether 4C8 does or does not possess the same functional and/or binding properties as the claimed antibodies without such a showing.

The prior art teaching anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 27, 28 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watanabe et al (J. Imm. Meth. [1995] 185:19-29; cited on form PTO-1449 filed 10/15/04) as applied to claim 1 above, and further in view of U.S. Patent No. 5,480,974 to Morgan et al (A on form PTO-892).

Watanabe has been discussed supra.

Watanabe does not disclose chimeric antibodies or IgG2a/G3 antibodies.

The '974 patent teaches a different monoclonal antibody directed at a different extracellular region of the C5aR, specifically, the N-terminal portion of the receptor (see Figure 13 and column 7, lines 36-41 in particular). The '974 patent teaches making a chimeric or CDR-grafted form of the anti-C5aR antibody (column 6, line 61, to column 7, line 35 in particular) [claim 27].

The '974 patent further teaches that under some circumstances, monoclonal antibodies of one isotype might be preferable over another. Accordingly, the '974 patent teaches isotype class switching in order to obtain an IgG2a or IgG3 form of the antibody (column 7, lines 43-61 in particular)[claim 28].

The '974 patent teaches that these variant forms of anti-C5aR antibodies are made recombinantly by methods well known in the art (columns 5-7 in particular)[claim 38].

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to make a chimeric form of the 4C8 antibody taught by Watanabe based upon the teachings of the '974 patent. One would have been motivated to make this change with a reasonable expectation of success because it would provide the artisan with chimeric forms of antibodies specific for two different antigenic determinants of the C5aR for therapeutic and/or in vivo diagnostic purposes. One would have been further motivated to make an IgG2a or IgG3 form of the 4C8 antibody with a reasonable

expectation of success based upon the teachings of the '974 patent that some isotypes can be preferable over others due to diagnostic or therapeutic efficacy and that IgG2a and IgG3 antibodies actively participate in the cytolytic destruction of target cells (column 7, lines 43-61 in particular).

7. Claims 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watanabe et al (J. Imm. Meth. [1995] 185:19-29; cited on form PTO-1449 filed 10/15/04) as applied to claim 1 above, and further in view of FitzGerald (Meth. Enzymol [1987] 151:139-145; U on form PTO-892).

Watanabe has been discussed supra.

Watanabe does not disclose a conjugate with a toxic agent, such as a *Pseudomonas* exotoxin.

FitzGerald teaches conjugating antibodies with *Pseudomonas* exotoxin A in order to kill cells that the antibody is specific for (see entire document, pages 139-140 in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to conjugate the 4C8 antibody to *Pseudomonas* exotoxin A using the method of FitzGerald. One would have been motivated to combine the teachings with a reasonable expectation of success by the teachings of FitzGerald that such immunotoxins can be used to specifically eliminate cells bearing C5aR from a biological sample.

Conclusion

8. Claims 29-32 and 52-54 are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571)272-0852. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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